

What is claimed is:

1. A method for identifying a molecule that reduces a polypeptide variance between two biological samples, which comprises:
  - contacting a first biological sample with one or more inactivated enzymes in a first system;
  - contacting a second biological sample with the one or more inactivated enzymes and one or more test molecules in a second system, wherein the one or more inactivated enzymes are capable of binding to a native polypeptide substrate or a fragment thereof and are catalytically defective, and wherein one or more of the inactivated enzymes are capable of detecting the presence of a polypeptide variance between the two biological samples;
  - detecting a signal corresponding to a polypeptide bound to the one or more inactivated enzymes in the second system and comparing the signal with a corresponding signal in the first system, whereby a test molecule that reduces the difference between the signals relative to the difference between the signals in the absence of the test compound is identified as a molecule that modulates a polypeptide variance between two biological samples.
2. The method of claim 1, wherein the molecule that modulates a polypeptide variance negates the difference between the signal from the first system and the signal from the second system.
3. The method of claim 1, wherein the inactivated enzyme is capable of binding to a binding site on the native polypeptide substrate or fragment thereof that comprises a modification capable of being added to the polypeptide by a native post-translational modification process.
4. The method of claim 3, wherein the modification is a phosphate moiety, ubiquitin moiety or acetyl moiety.
5. The method of claim 1, wherein the inactivated enzyme is a modified protein phosphatase, a modified deubiquitinase, a modified deacetylase, or a functional fragment thereof.
6. The method of claim 1, wherein the first system and/or second system comprise one or more inactivated enzymes incapable of detecting the presence of a polypeptide variance between the two biological samples in the absence of the one or more test molecules.
7. The method of claim 1, wherein a system is a well in a microtiter plate.
8. The method of claim 1, wherein one biological sample is contacted with one or more substances that are not contacted with the other biological sample.

9. The method of claim 8, wherein the one or more substances are selected from the group consisting of exogenous erythropoietin, exogenous TNF-alpha, exogenous toxin, an exogenous antimetastatic molecule and an exogenous antineoplastic molecule.
10. The method of claim 1, wherein one biological sample comprises cancerous cells and the other biological sample does not.
11. The method of claim 1, wherein the signal is a mass spectrometric signal.
12. The method of claim 11, wherein the signal is a MALDI-TOF signal.
13. An array comprising two or more inactivated enzymes immobilized to a solid support, wherein each inactivated enzyme is capable of binding to a native polypeptide substrate or a fragment thereof and is catalytically defective.
14. The array of claim 13, wherein one or more of the inactivated enzymes are capable of binding to a binding site on the native polypeptide substrate or fragment thereof that comprises a modification capable of being added to the polypeptide by a native post-translational modification process.
15. The array of claim 13, wherein one or more of the inactivated enzymes are capable of detecting the presence of a polypeptide variance between two biological samples.
16. The array of claim 13, wherein one or more of the inactivated enzymes is a modified phosphatase, a modified deubiquitinase, a modified deacetylase, or a functional fragment thereof.
17. The array of claim 13, wherein the solid support is a microtiter plate.
18. The array of claim 17, wherein one or more wells in the microtiter plate comprise one or more inactivated enzymes capable of detecting the presence of a polypeptide variance between two biological samples.
19. The array of claim 17, wherein one or more wells in the microtiter plate comprise one or more inactivated enzymes not capable of detecting the presence of a polypeptide variance between two biological samples.
20. The array of claim 17, wherein one or more wells in the microtiter plate comprise one or more inactivated enzymes capable of detecting the presence of a polypeptide variance between two

biological samples and one or more inactivated enzymes not capable of detecting the presence of a polypeptide variance between two biological samples.

21. The array of claim 13, which comprises five or more inactivated enzymes.

22. A system comprising the array of claim 13 and a mass spectrometer.

23. A method for constructing an array of inactivated enzymes, which comprises:

contacting a first biological sample with inactivated enzymes in a first system;

contacting a second biological sample with the inactivated enzymes in a second system, wherein the inactivated enzymes are capable of binding to a native polypeptide substrate or a fragment thereof and are catalytically defective;

detecting and comparing signals corresponding to polypeptides bound to the inactivated enzymes in the first system and signals corresponding to polypeptides bound to the inactivated enzymes in the second system;

identifying inactivated enzymes for which there is a difference between a signal in the first system and a signal in the second system as informative inactivated enzymes and identifying inactivated enzymes for which there is no detectable difference between the signals as uninformative inactivated enzymes; and

depositing one or more of the informative inactivated enzymes in an array.

24. The method of claim 23, wherein the array comprises five or more inactivated enzymes.

25. The method of claim 23, which further comprises depositing one or more uninformative inactivated enzymes in the array.

26. The method of claim 25, wherein the array comprises five or more inactivated enzymes.

27. The method of claim 23, which further comprises depositing uninformative inactivated enzymes in a separate array.

28. The method of claim 27, wherein the separate array comprises five or more inactivated enzymes.